## REMARKS

Claims 1-4, 6, 9-12, 14, and 23-26 are pending in this application. Claims 1-4, 6, 9-12, 14, and 23-26 were variously rejected under 35 U.S.C. § 112, second paragraph. Claims 1-4, 6, 9-12, 14, and 23-26 were variously rejected under 35 U.S.C. § 112, first paragraph. Claims 1-3, 6, 9-11, and 23-26 were variously rejected under 35 U.S.C. § 103.

With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-4, 6, 9-12, 14, and 23-26 were variously rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse these rejections.

With regard to claims 1-4, 6, 9-12, 14, and 23-26, the Examiner states that it is unclear "if the claimed invention is directed to the treatment of any symptom of papillomavirus infection, or is limited to the treatment of the lesions associated with the infection." Office Action, page 3.

The claimed methods clearly involve administration of an ISS-containing polynucleotide at the site of a papillomavirus-associated lesion in an amount sufficient to delay development or to reduce severity of a symptom of papillomavirus infection. The claims are not limited to delaying development or reducing severity of the particular papillomavirus-associated lesion to which the

ISS-containing polynucleotide is administered. Indeed, the Office has acknowledged that "administration of ISS at the site of one lesion can effect regression of an untreated lesion in the same animal." Office Action, mailed December 2, 2003, paragraph bridging pages 3-4. Applicants respectfully submit that the pending claims are definite and no clarification of the claim language is required.

With regard to claims 1-4, 6, 23, and 24, the Examiner states that "it is unclear how the ISS can both delay the development of a lesion and be administered to the site of the lesion. This is because the ISS cannot be administered to the site of the lesion if it has not yet been formed." Office Action, page 3.

The claims clearly state that "said composition is administered at a papillomavirus-associated lesion." Thus, a papillomavirus-associated lesion is present at the time of administration. Applicants respectfully submit that the pending claims are definite and no clarification of the claim language is required.

Contrary to the Examiner's assertion in this rejection that "the Applicant has not disclosed what other symptoms may be treated other than the lesion themselves," the specification provides examples of symptoms of papillomavirus infection beyond a particular lesion. This is discussed further herein where the written description rejection is addressed.

Applicants respectfully submit that the claims are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art. The claims are directed to a method of delaying development of a symptom of papillomavirus infection and to a method of reducing severity of a symptom of papillomavirus infection. The claimed methods involve administration of an ISS-containing polynucleotide at the site of a papillomavirus-associated lesion.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-3, 6, 9-11, and 23-26 were variously rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description and enablement requirements. Applicants respectfully traverse these rejections.

*Enablement*

Claims 1-4, 6, 23, and 24 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

As an initial matter, Applicants acknowledge, with appreciation, withdrawal of this rejection for claims 9-12, 25, and 26.

This rejection has been maintained with respect to claim 1-4, 6, 23, and 24 since "it is assumed that the claims still read on methods of administering the ISS prior to the onset of the lesion formation." Office Action, page 5.

As discussed above, the claims clearly state that "said composition is administered at a papillomavirus-associated lesion." Thus, a papillomavirus-associated lesion is present at the time of administration. In addition, the specification states that ""delaying" development of a viral infection or a symptom of viral infection means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease or symptom." Specification page 15, lines 15-18.

Applicants have provided experimental results[1] demonstrating that, upon administration of a claimed composition to a papillomavirus-associated lesion, growth of a papilloma is slowed, *i.e.*, delaying development of a symptom of papillomavirus infection.

Thus, Applicants submit that the claimed invention is enabled by the specification.

[1] See, for example, Example 2 and Figure 3 of the specification and the experiments and Exhibit A of the Declaration of Dr. Van Nest, submitted September 3, 2003.

*Written Description*

Claims 1-4, 6, 9-12, and 23-26 were rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner bases this rejection on an alleged lack of written description support for the scope of "a symptom of papillomavirus infection" and cites *Eli Lilly and Co.*, 43 USPQ2d 1406. The Examiner asserts that "the only types of symptoms identified by the Applicant are those involving the formation of lesions. The Applicant has neither provided examples of other types of symptoms, or provided any indication that such other symptoms may be treated by the administration of an ISS as described in the claims." Office Action, page 6. Applicants respectfully disagree.

Quoting from the Office's Written Description Requirement Guidelines, the court in *Enzo* stated that "the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added)." *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

Applicants respectfully point out that the specification provides examples of symptoms of papillomavirus infection in addition to papillomavirus-associated lesions. For example, at page 14, lines 18-24, the specification describes that, in addition to lesions, symptoms of papillomavirus infection include secondary symptoms associated with lesions, such as "hoarseness of voice, breathing difficulties, pain and discomfort." At pages 39-41, the specification describes that symptoms of papillomavirus infection can include cellular atypia and subcellular changes, such dysplasia and nuclear enlargement, hyperchromasia and/or pyknosis. Thus, the specification describes symptoms in addition to papillomavirus-associated lesions.

In addition, Applicants respectfully submit that symptoms of papillomavirus infection were well known in the art at the time the instant application was filed. For example, Bauman, cited by the Examiner, describes a variety of symptoms associated with recurrent papillomavirus infection of the aerodigestive tract.[2]

Thus, disclosed in the specification, and known in the art, are symptoms of papillomavirus infection such that a skilled artisan would recognize possession of the claimed invention. Accordingly, Applicants respectfully submit that the written description requirement has been met.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §103

Claims 1-3, 6, 9-11, and 23-26 were rejected under 35 U.S.C. §103 as allegedly unpatentable over the teachings of Beutner *et al.* (1998, *J. Am. Acad. Dermatol.* 38(2/1) 230-239; "Beutner") and Bauman *et al.* (1996, *Pediatr. Clin. N. Am.* 43(6):1385-1401; "Bauman"), and further in view of the teachings of Yamamoto *et al.* (1994, *JPN J. Cancer Res.* 85:775-779; "Yamamoto"). Claims 4 and 12 were rejected under 35 U.S.C. §103 as allegedly unpatentable over the teachings of Beutner, Bauman, and Yamamoto and further in view of either Raz *et al.* (U.S. Pat. No. 6,514,948, "Raz") or Schwartz *et al.* (WO 98/55495; "Schwartz"). Applicants respectfully traverse these rejections.

A *prima facie* case of obviousness requires that three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

[2] See, for example, pages 1387-1389 of Bauman et al., 1996, *Pediatric Clinics of North America*, vol. 43, no. 6, pages 1385-1401 ("Bauman").

reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established. As presented below, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

The claimed invention is directed to administration of a composition comprising an ISS-containing polynucleotide at the site of a papillomavirus-associated lesion in an amount sufficient to delay development or to reduce severity of a symptom of papillomavirus infection. In the claimed methods, the ISS comprises the sequence 5'-C G pyrimidine pyrimidine C G-3'.

Bauman discusses at least 8 different therapies for the treatment of recurrent respiratory papillomatosis, one including administration of IFN-α. Beutner describes the use of imiquimod in the treatment of genital warts. Beutner discusses the response rate with imiquimod and the response rates with other treatments including intralesional interferon treatment. On page 237, Beutner describes that imiquimod induces the production of IFN-α and a variety of other cytokines. Neither Bauman nor Beutner teach or suggest the administration of an immunostimulatory polynucleotide for treating papillomavirus infection.

Yamamoto describes that several immunostimulatory oligonucleotides can stimulate peripheral blood lymphocytes to produce IFN-α, IFN-β, and IFN-γ. At page 777, Yamamoto makes the general suggestion that the results presented therein "should aid the therapeutic application of MY-1 against cancer and viral infections." MY-1 is a mixture of oligonucleotides of undescribed nucleotide sequences extracted and purified from *Mycobacterium bovis* BCG. Yamamoto does not teach or suggest the use of a composition comprising immunostimulatory oligonucleotides for treating papillomavirus infection, much less the use of a composition comprising a polynucleotide as claimed.

The Examiner states that because Bauman and Beutner indicate that inducing IFN-α production "may be used for treatment of papillomavirus-associated lesions, it would have been obvious to those in the art to use the oligonucleotide adjuvants of Yamamoto in such a method." Office Action, page 8. Applicants respectfully disagree with this conclusion and submit that the combination of Bauman, Beutner and Yamamoto do not provide any suggestion or motivation to modify the teachings therein to arrive at the claimed invention.

The Examiner appears to be relying on an alleged equivalence of the imiquimod of Beutner, the IFN-α of Bauman, and immunostimulatory oligonucleotides of Yamamoto as a rationale supporting this rejection. However, in order to rely on equivalence in this rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. M.P.E.P. §2144.06; *In re Ruff*, 256F.2d 590, 118 USPQ 340 (CCPA 1958).

Beutner teaches that imiquimod induces the production of a variety of cytokines, one of which is IFN-α, and Yamamoto teaches that particular immunostimulatory oligonucleotides can induce the production of a variety of IFNs, one of which is IFN-α. Even though these entirely different substances can each induce production of IFN-α, the references also assign many other activities to the substances, suggesting that each would induce different effects upon administration. Thus, the cited references do not support an equivalence of the imiquimod and immunostimulatory oligonucleotides and do not render substitution of an immunostimulatory oligonucleotide for the imiquimod obvious.

Bauman discusses administration of IFN-α for the treatment of recurrent respiratory papillomatosis. As Yamamoto indicates, particular immunostimulatory oligonucleotides can induce the production of a variety of interferons as well as stimulate other activities. Thus, the cited references do not render substitution of an immunostimulatory oligonucleotide for the IFN-α equivalent or obvious.

Even if it is suggested that a motivation to combine the references exists, which Applicants decidedly do not, the combination of references provide an 'obvious to try' situation at most. The court has "consistently held that 'obvious-to-try' is not to be equated with obviousness under 35 U.S.C. 103." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990).

An 'obvious-to-try' situation exists where a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosures, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). Applicants respectfully submit that Yamamoto's general teaching that some immunostimulatory oligonucleotides stimulate the production of interferons in cells in culture is not sufficient teaching that delaying development or reducing severity of a symptom of papillomavirus infection would result from administration of the claimed composition.

The Examiner finds a reasonable expectation of success "due to the teachings regarding IFN-α induction in Beutner and Bauman, and the fact that the Yamamoto adjuvant was know to be able to induce this cytokine." Office Action, page 8. Applicants respectfully disagree with this conclusion. Since the references teach different activities for the respective compounds, the combination of references do not provide a reasonable expectation of success with regard to the claimed invention.

Further, Applicants respectfully submit that, even if combined, the cited references do not teach or suggest all of the claim limitations. None of the references teach or suggest the use of an immunostimulatory sequence comprising 5'-C G pyrimidine pyrimidine C G-3'.

Contrary to the Examiner statement that "Yamamoto teaches that an immunostimulatory sequence comprising the sequence AACGTTCG was a strong inducer of IFN-α,"[3] Applicants

[3] Office Action, page 8.

respectfully point out that none of the oligonucleotides taught in Yamamoto include this sequence or the claimed immunostimulatory sequence. Thus, even combined, the references do not teach or suggest all of the limitations of the claimed invention. Thus, the references do not render the claimed invention obvious.

Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established over Beutner and Bauman and further in view of Yamamoto.

Claims 4 and 12 were rejected over Beutner, Bauman and Yamamoto and further in view of Raz or Schwartz. Raz and Schwartz describe modulating an immune response with an immunostimulatory sequence of SEQ ID NO:1. Neither Raz nor Schwartz teach or suggest the use of immunostimulatory sequences for delaying development or reducing severity of a symptom of papillomavirus infection.

Thus, Raz and Schwartz do not supply what is missing from the primary references, Beutner, Bauman, and Yamamoto. The combination of Beutner, Bauman, and Yamamoto and the secondary references do not provide any suggestion or motivation to modify the teachings therein to arrive at the claimed invention and, thus, do not render the claimed invention obvious. In addition, the references do not provide a reasonable expectation of success of the claimed invention. Thus, a *prima facie* case of obviousness has not been established for the cited references.

In sum, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

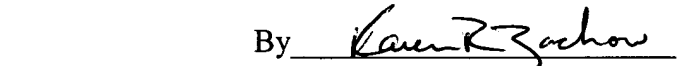
## CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001300.

Dated: October 12, 2004

Respectfully submitted,

By 

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